Mr. Richard Jansen, Pharm.D. SEPTEMBER 20, 1996
Vice President
Regulatory and Clinical Affairs
Spine-Tech, Inc.
7375 Bush Lake Road
Minneapolis, Minnesota 55439-2029

Re: P950002
BAK™ Interbody Fusion System with instrumentation
Filed: August 28, 1995
Amended: February 22, 1996; April 15, 1996; April 19, 1996; April 22, 1996; May 10, 1996; July 26, 1996; August 12, 1996; August 23, 1996; September 11, 1996; and September 13 , 1996.

Dear Dr. Jansen:

The Center for Devices and Radiological Health (CDRH) of the Food a nd Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the BAK™ Interbod y Fusion System with instrumentation. The device is indicated for use with autogenous bone graft in patients with degenerative disc disease (DDD) at one or two contiguous levels from L2-S1. These DDD patients may also have up to Grade I spondylolisthesis or retrolisthesis at the involved level(s). BAK™ devices are to be implanted via an open anterior or posterior approach.

DDD is defined as discogenic back pain with degeneration of the disc confirmed by history an d radiographic studies. These patients should be skeletally mature and have had six months of non - operative treatment.

We are pleased to inform you that the PMA is approv ed subject to the conditions described below and in the "Conditions of Approval" (enclosed) and the following condition that you provide update d promotional and advertising materials in your annual report s. You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of sec tion 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(i i) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning o f section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in thi s order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the post-approval requirements in the enclosure, the post-approval reports must include the following information:

1. In order to assess the long-term performance of the BAK™ Interbody Fusion System, please conduct a post-approval study to obtain a total of 6 years of postoperative data from a minimum of 100 patients from each surgical approach group (i.e., anterior and posterior). These outcomes should be submitted to the FDA as part of your annual report. As stated in your PMA amendment received by FDA on September 11, 1996, your post-approval study will incorporate the following elements:

    a. inclusion of 150 patients implanted from the anterior approach and 150 patients implanted from the posterior approach. Patients will be selected from 3 to 6 sites which participated in the original IDE study. With an approximate 10% loss of patients to follow-up per each of the remaining four years, this should yield a minimum of 100 patients per anterior and posterior approach;

    b. collection of the following information biennially for each patient (because the designated patient population has already reached the two-year time point, patients will be evaluated at his/her 4 and 6-year time points):

        (1) a description of any surgical interventions which include reoperations, removals, revisions, and supplemental fixations;

        (2) radiographic assessment of fusion evaluated by an independent radiologist;

        (3) clinical assessment of pain and function using the scales employed in the original IDE study;

    c. use of following mechanisms to inform the patient of the post-approval study and to better assure an adequate number of patients are available at the completion of the study:

        (1) patient agreement to participate in the post-approval study by patient signing Letter of Agreement;

        (2) letters to participating physicians notifying them of impending due dates for patient assessment;

        (3) reimbursement for the physician and/or patient, as necessary;

        (4) reimbursement for costs of x-rays and/or physician office visits by patient's insurance and/or by Spine-Tech, Inc.; and

    d. annual assessment of physician compliance with the study.

2. Because of the unknown long-term device performance, particularly the resulting bony fusion characteristics, please conduct a post-approval study that focusses on the retrieval analyses

of any BAK™ device that is implanted and subsequently removed. This post-approval study is not limited to the patient population described in item 1 above. Histological information (e.g., bony ingrowth quality, bone quantity, response to potential wear debris, etc.) and metallurgical information (e.g., metal wear, deformation, cracking, corrosion, etc.) should be collected and reported in the annual reports. This post-approval study should continue for the duration of the study described in item 1 above.

Please note that the data obtained in these post-approval studies must be reflected in the labeling (via a PMA supplement) when they are completed.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling (i.e., package labels, package insert, patient information brochure, and surgical technique manuals) in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Mr. Mark N. Melkerson, Chief of the Orthopedic Devices Branch at (301) 594-2036.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

DEVICE GENERIC NAME:	Intervertebral Body Fusion Device
DEVICE TRADE NAME:	BAK™ Interbody Fusion System
APPLICANT'S NAME:	Spine-Tech, Inc. 7375 Bush Lake Road Minneapolis, MN 55439-2029
PREMARKET APPROVAL (PMA) APPLICATION NUMBER:	P950002
DATE OF PANEL RECOMMENDATION:	May 23, 1996
DATE OF NOTICE OF APPROVAL TO THE APPLICANT:	September 20, 1996

II. INDICATIONS FOR USE

The BAK™ Interbody Fusion System is indicated for use with autogenous bone graft in patients with degenerative disc disease (DDD) at one or two contiguous levels from L2-S1. These DDD patients may also have up to Grade I spondylolisthesis or retrolisthesis at the involved level(s). BAK™ devices are to be implanted via an open anterior or posterior approach.

DDD is defined as discogenic back pain with degeneration of the disc confirmed by history and radiographic studies. These patients should be skeletally mature and have had six months of non-operative treatment.

III. DEVICE DESCRIPTION

The BAK™ device is a hollow, threaded cylinder available in five sizes. The sizes (diameter x length) are: 13mm x 20mm; 15mm x 20mm; 15mm x 24mm; 17mm x 24mm; and 17mm x 28mm. Each device has 10° modified square threads covering the entire outer surface of the implant and the first 5mm of one end of each device is tapered to allow for easier insertion into a pre-tapped intervertebral cavity. Each device has two large through-holes which are placed cephalad and caudad and multiple small transverse holes to enhance bony ingrowth. The BAK™ device may be used with an optional endcap which is available in corresponding diameters of 13mm, 15mm, and 17mm.

The BAK™ device is manufactured from titanium 6Al-4V (extra low interstitial) alloy which conforms to American Society Testing and Materials (ASTM) F136-92. The endcaps are manufactured from ultra-high molecular weight polyethylene (UHMWPe) which conforms to ASTM F648-84. The BAK™ device and endcap are provided sterile.

The BAK™ device and endcaps are implanted using a defined set of instruments. While some of the instruments are specific to either the anterior or posterior surgical approach, many of the instruments are common between the two surgical approaches. The instruments used for the anterior surgical approach include the following: anterior alignment guide; 8mm drill; distraction plug inserter; distraction plugs; guide pin; slap hammer; drill tube sheath; alignment guide handle; short series spacer; T-handle; starter reamer; final reamer; drill tube sleeve; guide pin; pituitary rongeur; drill tube sheath; trail implant; bone tap; implant driver; and endcap inserter. The instruments used for the posterior surgical approach include the following: starter alignment guide; alignment guide handle; 8mm drill; 8mm drill tube; distraction plug inserter; distraction plugs; drill tube guide; drill tube; guide pin; posterior drill tube sheath; slap hammer; short series spacer; T-handle; starter reamer; guide pin; final reamer; pituitary rongeur; trail implant; bone tap; implant driver; and endcap inserter. All instruments are manufactured from stainless steel which conforms to ASTM F899-94. All instruments are provided nonsterile and must be sterilized prior to use or reuse.

IV. CONTRAINDICATIONS

BAK™ implants should not be implanted in patients with an active infection at the operative site.

V. PRECAUTIONS

The surgeon should only implant the BAK™ device after adequate training and familiarity with the surgical technique manual.

Safety and effectiveness have not been established in patients with the following conditions: gross obesity; three or more levels to be fused; symptomatic cardiac disease; pregnancy; previous fusion attempt at the involved level(s); spondylolisthesis or retrolisthesis of Grade II or greater; systemic or terminal illness; significant loss of quantity or quality of vertebral bone stock usually due to osteoporosis or osteomalacia; conditions requiring steroid use; or active drug abuse.

Two devices should be implanted at each surgical level whenever possible. One device may be used if patient anatomy or surgical exposure does not allow for placement of two devices.

The BAK™ implant and endcap are supplied sterile and should be handled in a manner to avoid contamination. In the event of damage to the sterile packaging or inadvertent contamination, implants may be steam sterilized using a gravity cycle of 270°F for 3 minutes. The endcaps should not be re-sterilized if contaminated.

No implant or endcap should be re-used if it has come into contact with human tissue or bodily fluid.
Instruments for implantation of the BAK™ device are provided non-sterile and must be

sterilized prior to use. They may be sterilized using gravity steam at 270°F for 10 minutes or 250°F for 15 minutes.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Nonoperative alternative treatments may include, but are not limited to, physical therapy, medications, braces, chiropractic care, or exercise programs. In addition, there are alternative spinal fusion techniques. These include, but are not limited to, posterior lumbar interbody fusion (PLIF) procedures without instrumentation, anterior lumbar interbody fusion (ALIF) procedures without instrumentation, combined anterior and posterolateral (360°) fusion procedures, anterior/anterolateral spinal systems (e.g., plate and screw systems), or posterior spinal systems (e.g., hook and rod systems).

VII. POTENTIAL ADVERSE EFFECTS

From the investigational device exemption (IDE) G900193, a total of 947 patients were evaluated for adverse events with the BAK™ Interbody Fusion System. The adverse events (complications) were stratified by those that did not require surgical intervention and those that did. Further, because not all of the patients entered into the study had reached their 24 month postoperative time point, a time course distribution of the complications was provided. The intervals are as follows: operative (day of surgery); post-operative (first day post-op up to 2 months); 3 month (2 to 5 months); 6 month (5 to 9 months); 12 month (9 to 19 months); and 24 month (19 to 30 months). The overall rate was determined by adding the rates from the operative time point to 24 months. The rates shown in Table 1 below are the patient rates (i.e., number of patients with a particular complication divided by the total number of patients with available data at a given time point).

Table 1 - Complication Rates

	Op. N=947	Post-Op N=947	3 mo N=847	6 mo N=770	12 mo N=661	24 mo N=283	Overall Rate
Complications not requiring surgical intervention							
dura related	3.1%	0%	0%	0%	0.2%*	0%	3.3%
neurologic	1.9%	0.2%	0.4%	0.4%*	0%	0%	2.9%
infection	0%	2.1%	0.2%	0%	0.1%*	0%	2.4%
implant migration	0%	0.3%	0.9%	0.4%	0%	0%	1.6%
ileus	0.4%	1.1%	0%	0%	0%	0%	1.5%
vessel damage, bleeding	1.5%	0%	0%	0%	0%	0%	1.5%

atelectasis, pneumonia	0%	1.2%	0.1%	0%	0%	0%	1.3%
hematoma, seroma	0.1%	1.0%	0.1%	0.1%	0%	0%	1.3%
retrograde ejaculation	0.2%	0.1%	0.7%	0.3%	0%	0%	1.3%
other**	0.1%	0.7%	0%	0.1%	0.1%	0.3%	1.3%
urologic, swollen testicle, prostatic, epididymitis	0.2%	0.6%	0.1%	0%	0%	0%	0.9%
wound dehiscence, incisional hernia	0%	0.4%	0.1%	0.1%	0.1%	0%	0.7%
thrombophlebitis, embolism	0%	0.5%	0.2%	0%	0%	0%	0.7%
leg pain	0.1%	0.1%	0.1%	0%	0%	0.3%*	0.6%
*Complications requiring surgical intervention****							
additional stabilization	0%	0.2%	0.3%	0.6%	1.5%	2.1%	4.7%
additional level fusion	0%	0%	0.1%	0.1%	0.8%	0.7%	1.7%
implant migration	0%	0.6%	0.5%	0.1%	0%	0%	1.2%
leg pain	0%	0.4%	0.1%	0.1%	0.3%	0.3%	1.2%
dura related	0.5%	0%	0.1%	0%	0%	0%	0.6%
implant reposition	0%	0.3%	0%	0.1%	0%	0%	0.4%
other decompression	0%	0.1%	0%	0.1%	0%	0%	0.2%
anterior ligament penetration	0.1%	0%	0%	0%	0%	0%	0.1%
fractured sacrum	0%	0.1%	0%	0%	0%	0%	0.1%

*due to secondary surgical intervention

**other includes: anemia, colitis, gastro-intestinal (GI) bleeding, undisplaced sacral fracture, unrelated sacro-iliac joint infection, chronic subdural hematoma, umbilical hernia (unrelated to surgery), loose implant perioperatively, occipital infarction, possible pre-

existing disc space infection

***includes 9 revisions, 7 removals, 27 reoperations, and 26 supplemental fixations (see definitions below)

A revision is a procedure which adjusts or in any way modifies the original implant configuration (e.g., adjusting position of original configuration, removal with replacement of component). A removal is a procedure which removes one or more components of the original implant configuration without replacement of any components. A reoperation is a procedure which involves any surgical procedure at the involved level(s) which does not remove, modify, or add any components. A supplemental fixation is a procedure in which additional instrumentation not approved as part of the protocol is placed. This may include supplemental placement of a rod/screw system or a plate/screw system.

VIII. MARKETING HISTORY

The BAK™ Interbody Fusion System has been marketed in approximately 20 international countries. It has not been withdrawn from marketing for any reason relating to its safety or effectiveness.

IX. SUMMARY OF PRECLINICAL STUDIES

A. **Nonclinical Testing**

Nonclinical tests were conducted to characterize the mechanical properties of the BAK™ Interbody Fusion System. The smallest size BAK™ device (13mm x 20mm) was used for this testing because it represents the worst case device (thinnest internal web and thinnest cylindrical wall thickness) of the five sizes.

1. Ultimate Compressive Strength Testing

   A single BAK™ device was loaded statically in compression until implant failure or until 30,600 N (6876 lbs), the failure load of the jig, was reached. Five (5) devices sustained a static load of 30,600 N (6876 lbs) without failure. None of the five specimens were crushed or exhibited any cracking under microscopic examination following the testing. The device's compressive strength greatly exceeds the compressive strength of bone which is estimated to be approximately 1500 N (337 lbs).

2. Fatigue Testing

   A single BAK™ implant was loaded cyclically in compression at loads which ranged from 880 N (198 lbs) to 9600 N (2157 lbs) at 15 Hz. None of five (5) devices failed after 5 million cycles. Five million cycles typically represents the number of loading cycles a device might experience within two years. This

assumes moderate loading and the device's goal of stabilizing until fusion occurs within those two years. Because the device's compressive fatigue strength exceeds the static compressive strength of bone by at least a factor of six, the BAK™ device can be expected to withstand anticipated physiologic fatigue loads.

3. Polyethylene Endcap Pushout Test

This test was conducted to determine the static force required to dislodge the endcap from a BAK™ device. After the endcap was snap-fit to the BAK™ device, an axial load was applied through the cavity of the BAK™ device to the endcap. The average push-out load determined for five (5) samples was 111 ± 53 N (25 ± 12 lbs). Based on the expected minimal loading on the endcap, the endcap should not become dislodged from the BAK™ device.

B. **Stability Testing**

Three tests were performed to determine the effect of the device on the flexion/extension (F/E) and lateral stability of the spine after implantation of either one or two BAK™ devices. Bovine, porcine, and primate spines were used in these tests.

1. The first test was conducted to determine the effect of implanting one and two BAK™ devices on spinal stability, relative to the intact spine. One BAK™ device was implanted in a bovine spine (n=7) and two BAK™ devices were implanted in a porcine spine (n=2) and the flexion/extension and lateral stiffness of the spines were measured. Results with one device implanted showed that the spinal segments had an increased stiffness of 71% for flexion/extension and 77% for lateral bending relative to the same tests in spinal segments without implants. Results with two devices implanted showed that the spinal segments had an increased stiffness of 81% for flexion/extension and 477% for lateral bending relative to the same tests in spinal segments without implants. Therefore, the implantation of either one or two devices increased the initial spinal stability.

2. The second test was designed to compare the initial biomechanical stability of the following constructs in a calf spine model: 1) BAK™ implant; 2) PLIF with iliac crest bone graft alone; 3) PLIF with rigid posterior instrumentation; 4) BAK™ implant with rigid posterior instrumentation; and 5) rigid posterior instrumentation (pedicle screws). Non-destructive testing was performed on eight (8) lumbar (L3-L4) calf spines of similar age and size. Each specimen was tested for stiffness in flexion/extension, torsion, and axial loading using the intact spine as a baseline and the five constructs above.

The BAK™ system, used alone, doubled the stiffness of the intact spine in terms of flexion/extension loading (2.6 versus 1.3 Nm/deg) and torsional loading (14 versus 7.5 Nm/deg) and did not migrate during testing. This BAK™ construct was stiffer than the PLIF with iliac crest bone graft alone (which had a

flexion/extension stiffness of 1 Nm/deg and a torsional stiffness of 5 Nm/deg) and was similar in stiffness to the PLIF with rigid posterior instrumentation (which had a flexion/extension stiffness of 2.9 Nm/deg and a torsional stiffness of 12.5 Nm/deg). The BAK™ increased the initial stiffness of a calf spine motion segment relative to the intact spine and compares favorably to the other stabilization methods with respect to initial spinal stability.

3. The third test assessed the mechanical flexibility of the motion segment both before and after instrumentation using the BAK™ device in a Chagma baboon model. Testing was performed on six (6) Chagma baboon spines at the L4-L5 motion segment. Each specimen was tested for stiffness in flexion and extension in its intact condition and with a single BAK™ implant. The six (6) instrumented lumbar segments showed a trend for increased stiffness in flexion ($p<0.07$). In the four comparisons made in extension, the instrumented segments were stiffer ($p<0.05$). The BAK™ device increased the flexion/extension stiffness of the spine relative to the intact spine.

C. **Foraminal Volume Study**

The objective of this study was to quantitatively assess changes in the size of the neuroforamen after anterior distraction using the BAK™ Interbody Fusion System in degenerated cadaveric lumbar spines. Nine (9) fresh frozen degenerative cadaver lumbar spines were obtained for the study. Anteroposterior and lateral x-rays were taken for each specimen with neuroforaminal stenosis at L4-L5 and L5-S1. The lateral x-rays were used to measure the anterior and posterior disc heights before and after insertion of the BAK™ implants. Measurements of the volumes and areas were conducted before and after anterior application of the BAK™ implants using three techniques: blunt probe; silicone mold; and computerized tomography. All data were normalized to the pre-implantation measurements.

After BAK™ implantation, the anterior disc heights increased 35.2 ± 19.2% at L4-L5 and 28.4 ± 12.0% at L5-S1 ($p<0.001$); the posterior disc heights increased 37.1 ± 20.9% at L4-L5 and 45.1 ± 28.0% at L5-S1 ($p<0.001$). The neuroforamen diameters measured with the blunt probe increased 13.3 ± 4.1% at L4-L5 and 12.3 ± 4.3% at L5-S1 after the BAK™ implantation. The areas measured by CT increased 29.0 ± 18.6% at L4-L5 and 33.8 ± 22.2% at L5-S1 after BAK™ implantation. The volume of each neuroforamen was calculated from the mass of the silicone mold and material density. The volumes increased 22.9 ± 8.3% at L4-L5 and 21.5 ± 11.5% at L5-S1. These results indicate that the BAK™ implant can increase the neuroforaminal volume and possibly reduce neuroforaminal stenosis.

X. SUMMARY OF ANIMAL STUDIES

A. **Horse Studies**

Studies involving the Bagby Basket, a smooth, stainless steel cylinder with transverse holes, as an interbody fusion device were conducted.

1. The first study involved the use of the Bagby Basket in stabilizing equine cervical vertebra. The goal of this study was to compare commercially available xenograft with the Bagby Basket filled with local autograph bone for equine interbody fusion. 16 horses were assigned into one of two treatment groups, eight (8) received a dowel of bovine xenograft and eight (8) received the Bagby Basket. At six months postoperatively, the horses were sacrificed and the spines evaluated.

   Mobility studies produced an index value for evaluation of both treatment groups. The index value of the implant was representative of substantially less perceptible motion than the index of the grossly fibrous bovine xenografts. Implantation of the bovine xenograft and the implant resulted in different forms of vertebral fusion. The use of the implant with autogenous bone graft usually resulted in an osseous union and provided a superior fusion. Gross examination of the fusion sites on cut section revealed several differences. The sites in which bovine xenografts had been implanted were extremely pale and frequently contained gross evidence of fibrous connective tissue dispersed through the graft sites. There was minimal evidence of fibrous connective tissue dispersed through the Bagby Basket implantation sites. The autograft within the implant was more consistent with the color and texture of normal cancellous bone.

2. A second study was conducted to evaluate the clinical effectiveness of the Bagby Basket in decompressing caudal cervical spinal cord compression in the horse. In this test, eight (8) male horses with caudal cervical spinal cord compression were implanted with a single bone graft-filled Bagby Basket in an effort to fuse the intervertebral space at the level of compression. The horses were evaluated five months postoperatively by neurologic evaluation, radiology, myelography, CSF analysis, serology, virology and bacteriology. Neurologic exams were repeated 10 months postoperatively. This test showed that all of the implants appeared to have been incorporated in osseous arthrodesis and that this was effective in decompressing all horses by five months post-op. All other results (CSF analysis, serology, virology, and bacteriology) were normal, both preoperatively and postoperatively.

B. **Primate Study**

This study was undertaken to evaluate the safety and effectiveness of the BAK™ device when used in the Chagma baboon. The effectiveness in producing a stable lumbar interbody construct was measured by radiologic, biomechanics, and histologic methods.

Comparing the BAK™ device and fresh frozen allograft in this experimental model, it was found that: 1) the Chagma baboon is an adequate model in evaluating lumbar interbody fusion techniques; 2) radiologic assessment showed that disc height loss and

increased local kyphosis occurred over time in both groups, although the allografts stabilized earlier (6 weeks) compared to the BAK™ device (24 weeks); 3) biomechanical evaluation revealed no statistically significant differences between the two implant groups; 4) histologic findings confirmed bone ingrowth in the BAK™ group; and 5) the BAK™ Interbody Fusion System was found to be an adequate fusion technique compared to fresh-frozen allograft in this experimental model and justified further human clinical assessment.

XI. SUMMARY OF CLINICAL INVESTIGATIONS

A clinical study of the BAK™ Interbody Fusion System was conducted in accordance with approved IDE G900193.

A. **Objective**

The objective of the study was to determine the safety and effectiveness of the BAK™ Interbody Fusion System in stabilizing and fusing the affected vertebrae when compared to literature controls.

B. **Inclusion and Exclusion Criteria**

The inclusion criteria were males and females between the ages of 21 and 65 with a diagnosis of DDD at 1 or 2 contiguous levels from L2-S1. These patients may have had disc herniation and/or no greater than Grade I spondylolisthesis. Additionally, these patients were to have had six months of unresponsive, nonoperative treatment. Note that based on Panel input, the definition for DDD was refined to that reflected in Section II above, Indications for Use.

The exclusion criteria were as follows: patients with active infection; osteoporosis or osteomalacia; a medical condition that interfered with the postoperative management program; circulatory problems; symptomatic cardiac disease; active malignancy; gross obesity; Grade II or greater spondylolisthesis at involved spine levels; pregnancy; DDD affecting three or more spine motion segments; and the presence of more three of the following psycho-social factors: alcoholism; drug dependence; recent or pending divorce; high level of job dissatisfaction; pending litigation; depression; multiple unsuccessful surgeries; smoking one or more packs per day; or a Waddel score of three or more.

Patients meeting the inclusion criteria were stratified into four treatment groups by the surgical approach (i.e., open anterior or open posterior) and the number of involved levels (i.e., one or two).

- Anterior surgical approach involving one disc level (A1)
- Anterior surgical approach involving two disc levels (A2)
- Posterior surgical approach involving one disc level (P1)
- Posterior surgical approach involving two disc levels (P2)

For both surgical approaches, autogenous bone graft was packed into the BAK™ devices after implantation. If the disc space had sufficient room after devices placement, autogenous bone graft could be placed around them.

C. Patient Population and Demographics

The BAK™ study population is comprised of 54% (512/947) males and 46% (435/947) females. The mean age at the time of study enrollment was 41.5 years with a range of 20 to 73 years. 57% (544/947) of the patients were enrolled in the study with compensation related injuries. 36% (342/947) of the patients had prior back surgery. The average duration of back symptoms prior to enrollment in this study was 5.5 years.

All 947 patients enrolled in the BAK™ study had a diagnosis of DDD, 43% (408/947) with disc herniation and 57% (539/947) without herniation. Grade I spondylolisthesis or retrolisthesis (reverse spondylolisthesis) was present in 12% (112/947) of the population.

A total of 1317 levels were implanted in 947 patients. The distribution of the levels by patient were: <1% (5/947) at L2-L3; 5% (49/947) at L3-L4; 56% (530/947) at L4-L5; 38% (356/947) at L5-S1; <1% (4/947) at L5-L6; <1% (1/947) at L6-S1; and <1% (2/947) at L6-S1. Of the 947 patients, 62% (591/947) had one-level fusions and 38% (356/947) had two-level fusions. There were 55 single cages and 1262 pairs of cages implanted for a total of 2579 cages implanted.

D. Evaluation Schedule

Patients were evaluated preoperatively, immediately postoperatively (i.e., hospital discharge), at 3 months, 6 months, 12 months, 24 months, and biennially thereafter until the last patient had his/her two-year evaluation. Radiographic studies were conducted at 12 and 24 months postoperatively.

E. Patient Accountability

A total of 947 patients were enrolled at 19 investigational sites in the United States by 44 investigators. Of these 947 patients, there were 32% (305/947) in the A1 subgroup, 30% (286/947) in the A2 subgroup, 29% (272/947) in the P1 subgroup, and 9% (84/947) in the P2 subgroup. As of November, 1995, a total of 307 patients had reached his/her two-year postoperative time point. Follow-up evaluations, which included an assessment of fusion, pain, function and muscle strength, were performed on 283 of these 307 patients (92%). Complete follow-up evaluations (i.e., measurement of each of the four major outcome parameters) were performed on 254 of these 283 patients (90%). Partial follow-up evaluations were available for 29 patients (10%).

F. Study Design and Analyses

1. Literature Study Control

Literature controls were employed in this study. Outcomes of patients implanted with BAK™ devices via an anterior approach were compared to outcomes of patients who received ALIFs. Outcome of patients implanted with BAK™ devices via a posterior approach were compared to outcomes of patients who received PLIFs. Literature references were deemed acceptable as controls if at least 50% of patients had back pain due to DDD; this group may or may not have had spondylolisthesis of Grade I or less. This differs from the BAK™ group in which all patients had back pain due to DDD and had no greater than Grade I spondylolisthesis.

The literature controls used in this study had many differences relative to the BAK™ population with respect to the indication for use, the method by which DDD was assessed, the number of levels fused, the age of the patients, the types of outcome criteria assessed, the method of outcome assessment, the definitions for successful outcome, the duration and nature of follow-up, the incidence of previous back surgery at the same level, and whether the patients were affected by more than two psychological/behavioral risk factors (e.g., alcoholism, drug abuse).

Use of a literature control group was common at the time of the submission of this study, although it is now recognized as less desirable than a randomized, concurrent control study. The advantages of using a randomized, concurrent control reflects the disadvantages of literature controls. In general, in a randomized, concurrent control study, potential bias is eliminated or at least reduced, unknown or known baseline factors tend to be balanced between the two groups, the statistical properties of hypothetical tests are improved, time trends are controlled because of concurrency, and the results tend to be more successfully convincing.

2. Data Pooling

Pooling the data between investigational sites and other stratified groups were justified based on a statistical analyses using Pearson chi-squared tests or Fishers exact tests.

G. **Effectiveness Analyses**

The effectiveness variables included an assessment of fusion at the involved level(s), pain, function, and muscle strength; neurological information was captured in the safety assessment. In some cases, only partial data were available (i.e., not all of the four outcome measures were obtained for all patients at all follow-up points). In these cases, all available outcomes for fusion, pain, function, and muscle strength were summarized in these analyses. Therefore, the number of patients included in the assessment of the four outcomes varies slightly due to missing data. Because not all of the patients had reached his/her two-year postoperative time point, the effectiveness analyses involved both the 12 month and 24 month time points for comparison purposes.

H. **Effectiveness Analysis - Fusion**

Successful fusion was defined as less than 5° of motion on a flexion/extension series of x-rays at the involved level(s). In cases where two levels were implanted, both levels must have been fused in order for that patient to be considered fused. An independent radiologist reviewed the films. The successful fusion rates are provided in Table 2 below for each study subgroup and the overall population.

Table 2 - Successful Fusion Rates at 12 and 24 Months

Study Subgroups	12 Month Rate	24 Month Rate
Anterior, 1-level	92% (211/229)	98% (106/108)
Anterior, 2-levels	79% (118/150)	80% (56/70)
Posterior, 1-level	87% (156/180)	94% (68/72)
Posterior, 2-levels	75% (45/60)	71% (12/17)
All Study Subgroups	86% (530/619)	91% (242/267)

I. **Effectiveness Analysis - Pain**

Pain was measured on a 6-point scale where 1 = no recurrent episode of low back pain and able to perform all previous activities, 2 = occasional recurrence of low back pain, 3 = mild pain, 4 = moderate pain, 5 = marked pain, and 6 = disabling pain.

The distribution of pain scores preoperatively and at 24 months is shown in Table 3 below. One patient was missing the preoperative pain score.

Table 3 - Distribution of Pain Scores

Pain Level	Preoperative Rate	24 Month Rate
None (1)	0%	19% (54/280)
Episodic (2)	<1% (4/946)	18% (49/280)
Mild (3)	<1% (6/946)	27% (75/280)
Moderate (4)	22% (210/946)	24% (68/280)
Marked (5)	54% (506/946)	9% (25/280)
Disabled (6)	23% (220/946)	3% (9/280)

All patients experiencing an improvement by at least one level in the pain score relative to their preoperative score were considered to have a successful result in terms of the pain

outcome measure. Table 4 below shows the successful pain rates for each study subgroup and the overall population.

Table 4 - Successful Pain Rates at 12 and 24 Months

Study Subgroups	12 Month Rate	24 Month Rate
Anterior, 1-level	84% (202/240)	84% (93/111)
Anterior, 2-levels	88% (136/155)	86% (62/72)
Posterior, 1-level	81% (158/196)	87% (66/76)
Posterior, 2-levels	77% (48/62)	81% (17/21)
All Study Subgroups	83% (544/653)	85% (238/280)

It is important to distinguish between patients with a successful pain outcome and the amount of pain experienced by patients after implantation with the BAK™ device. A successful outcome did not necessarily mean that a patient experienced no pain; instead, it means that there was at least one level of improvement.

J. **Effectiveness Analysis - Function**

Function was measured on a 26-point scale which ranged from 7 (best) to 32 (worst) points. This function scale measures the patient's ability to perform activities of daily living (i.e., standing, sitting, walking, squatting, ability to put on shoes and socks), level of recreational activity, and level of employment.

The average preoperative function score was 20.9 ± 3.7 (range 9-32) for 946 patients; a preoperative function score was missing for one patient. The average function score at 24 months was 14.5 ± 4.5 for 280 patients.

All patients maintaining or experiencing an improvement by at least one point in the function score relative to their preoperative score, were considered to have a successful result in terms of the function outcome measure. Table 5 shows the successful function rates for each study subgroup and the overall population.

Table 5 - Successful Function Rates at 12 and 24 Months

Study Subgroups	12 Month Rate	24 Month Rate
Anterior, 1-level	93% (224/240)	95% (105/111)
Anterior, 2-levels	89% (138/155)	94% (68/72)
Posterior, 1-level	89% (174/196)	92% (70/76)
Posterior, 2-levels	89% (55/62)	95% (20/21)
All Study Subgroups	91% (591/653)	94% (263/280)

K. **Effectiveness Analysis - Muscle Strength**

Muscle strength was evaluated bilaterally at four sites: quadriceps, dorsiflexion-inversion, great toe extension, and plantarflexion. Each of the sites was measured an a 3-point scale ranging from 1 (normal) to 3 (marked decrease). The majority of patients (82%) demonstrated normal muscle strength preoperatively.

Maintenance or improvement in muscle strength for all eight sites evaluated was required to be considered a success. Table 6 shows the successful muscle strength rates for each study subgroup and the overall population.

Table 6 - Successful Muscle Strength Rates at 12 and 24 Months

Study Subgroups	12 Month Rate	24 Month Rate
Anterior, 1-level	92% (221/240)	94% (102/109)
Anterior, 2-levels	92% (135/147)	94% (64/68)
Posterior, 1-level	95% (176/185)	94% (67/71)
Posterior, 2-levels	92% (55/60)	100% (20/20)
All Study Subgroups	93% (587/629)	94% (253/268)

L. **Safety Analysis**

Safety analyses included all patients regardless of the completeness of their follow-up data or length of follow-up. Safety was assessed through physical examinations, x-rays, and by questioning of all patients enrolled in the study. For a summary of the safety data, please see Table 1 in Section VII above, Potential Adverse Effects.

M. **Study Success / Statistical Differences**

To be considered an overall study success, the patient must have met each of the

following four criteria: 1) fusion of the involved level(s); 2) improvement in pain; 3) maintenance or improvement in function; and 4) maintenance or improvement in muscle strength. The overall success rates at 12 and 24 months for each subgroup and the overall patient population are provided in Table 7 below. Note that the number of patients with data available differs slightly for each based on the study follow-up.

Table 7 - Study Success Rates at 12 and 24 Months

Study Subgroups	12 Month Rate	24 Month Rate
Anterior, 1-level	73% (163/223)	81% (85/105)
Anterior, 2-levels	64% (90/140)	59% (39/66)
Posterior, 1-level	64% (108/168)	78% (52/67)
Posterior, 2-levels	52% (30/58)	50% (8/16)
All Study Subgroups	66% (391/589)	72% (184/254)

The clinical utility of the BAK™ procedure also was evaluated by the proportion of patients that returned to work or were able to work. At the time of the initial BAK™ procedure, 36% of all patients were working full-time or part-time. The proportion of patients working was decreased to 30% at three months follow-up and then progressively increased to 44%, 54%, and 62% at 6, 12, and 24 month follow-up visits, respectively.

Because of the many differences between the literature control groups and the BAK™ group, the longitudinal analyses performed on the BAK™ patient population was extremely important in the assessment of the safety and effectiveness of the BAK™ device. The longitudinal analyses (using Generalized Estimating Equation (GEE) model) showed that the outcomes of fusion, pain, function, and muscle strength did not worsen over time for all study subgroups combined. Specifically, for the total patient population, the rate of fusion increased with time, the amount of pain decreased with time, and the patient's ability to function increased with time.

From the longitudinal analyses of these clinical data, the following statistical differences were observed among the study subgroups up to or at the two-year time point:

- The two year postoperative data indicates that the likelihood of needing additional supplemental fixation increases over time in patients who were not fused or showed no improvement in pain.

- For both the anterior and posterior approaches, patients with one level fusion had lower overall complication rates than patients with two level fusions.

- Patients implanted with the BAK™ device from the posterior approach had higher rates of intra-operative complications and early postoperative surgical interventions than patients implanted from the anterior approach.

- Patients implanted from the anterior approach had a higher overall rate of early postoperative complications than patients implanted from the posterior approach.

- For both the anterior and posterior approaches, patient who had higher preoperative baseline pain scores showed better pain improvement throughout the study than patients with lower baseline pain scores.

N. **Comparison with Literature Controls**

A total of 20 ALIF and 9 PLIF literature articles were used as controls; these are identified in Section XVI below, References. As previously discussed, these literature controls were often greatly different from the BAK™ population. However, clinical results and complication information were extracted for purposes of this comparison.

1. Anterior Results

As stated above, there were 20 ALIF literature control articles. The sample sizes reported in these articles ranged from 20 to 150. The data from the control articles were compared to the data from the BAK™ Interbody Fusion System for the total anterior patient population (i.e., A1 and A2) at 24 months.

The fusion rate for the BAK™ was 91% (162/178) for the anterior group. The range of fusion rates reported in the ALIF literature controls was 46% to 96%. Fusion results of the BAK™ were better than literature results in 18 of 20 articles, significantly better in 13, and none were significantly worse than the literature controls.

The definition of clinical success in the ALIF literature primarily involved an assessment of pain but occasionally included some work status, function, and narcotic use information. The clinical success rates reported in the ALIF literature ranged from 41% to 100%. Taking into consideration the same types of measurements, these literature control rates were compared to the following BAK™ clinical rates: 85% (155/183) for pain and 95% (173/183) for function. There were 22 possible assessments in the 20 ALIF literature controls. BAK™ clinical results were better than ALIF in 8 assessments, within 5% of the ALIF results in 3 assessments, and worse than the ALIF results in 11 assessments. It cannot be determined if the differences are due to true differences in clinical success, or due to differences in patient population, data collection, or interpretation of methods.

2. Posterior Results

As stated above, there were 9 PLIF literature control articles. The sample sizes reported in these articles ranged from 20 to 462. The data from the control articles were compared to the data from the BAK™ Interbody Fusion System for the total posterior patient population (i.e., P1 and P2) at 24 months.

The fusion rate for the BAK™ was 90% (80/89) for the posterior group. The range of fusion rates reported in literature was 74% to 96%. Fusion results for the BAK™ device were higher than 5 PLIF studies and statistically higher in 1. Although 4 of the PLIF studies reported results better than the BAK™, none of these differences were statistically significant. It is unclear if these differences are due to true differences in clinical success or due to differences in patient population, data collection or interpretation of methods.

As with the ALIF literature, the definition of clinical success in the PLIF literature primarily involved an assessment of pain but occasionally included some work status, function, and narcotic use information. The clinical success rates reported in the PLIF literature ranged from 60% to 94%. Taking into consideration the same types of measurements, these literature control rates were compared to the following BAK™ clinical rates: 86% (83/97) for pain and 93% (90/97) for function.

3. Comparison of Complications

The experience in this clinical investigation with the BAK™ system compares favorably with the ALIF and PLIF literature complication rates. Reported complications for the BAK™ system were within the range reported for the literature control groups.

XII. CONCLUSIONS DRAWN FROM THE STUDIES

The nonclinical (i.e., mechanical), animal, and clinical data provide reasonable assurance of the safety and effectiveness of the BAK™ Interbody Fusion System for the treatment of degeneration disc disease (DDD), when used as indicated.

XIII. PANEL RECOMMENDATION

The Orthopedic and Rehabilitation Devices Panel met to discuss the application on May 23, 1996. The Panel recommended that the application be approved pending submission to and approval by the Center for Devices and Radiological Health (CDRH) of: a reanalysis of the study outcomes with a revised definition of patient success; modifications to the labeling; creation of a patient information document; development of post-approval studies; continued follow-up of study patients; and completion of the IDE randomized study arm of the BAK™ Interbody Fusion System. The Panel agreed

with FDA's recommendation to define patient success as fusion of involved level(s); improvement in pain; maintenance or improvement in function; maintenance or improvement in muscle strength; and maintenance or improvement in neurological reflexes.

The Panel recommended that the labeling be modified to: (1) limit use to the treatment of patients with DDD where DDD is defined as back pain of discogenic origin with degeneration of the disc confirmed by historical and radiographic studies; (2) recommend a minimum of six months of non-operative treatment prior to surgery; (3) report the study's success rates and trends noted in the statistical analyses; (4) require that the device be packed with autograft bone; (5) limit implantation of the device to an open approach; and (6) limit use of the device to fusions involving one level or two adjacent levels.

As stated above, the Panel also recommended that two post-approval studies be developed. The first post-approval study is to obtain continued follow-up for a subset of the patients from the IDE study to evaluate the long-term device performance and patient outcomes for a minimum of five years. The second post-approval study is to retrieve and analyze any BAK™ device that was implanted and subsequently removed. The Panel recommended that retrieved implants be analyzed metallurgically and histologically for bone quality/quantity and potential wear debris.

XIV. CDRH DECISION

CDRH agreed with the Panel's recommendation that the PMA be approved subject to conditions and concurred with each of the conditions recommended by the Panel except for the recommendations to require continued follow-up of study patients and completion of the IDE randomized study arm of the BAK™ Interbody Fusion System. While CDRH agreed that it would be desirable to obtain long-term follow-up on the entire study population and the results of a randomized, concurrent clinical trial of the BAK™ device, sufficient information currently exists to approve this application. The Panel's recommendations were modified and made conditions of approval. In addition to the Panel's recommended conditions, CDRH also required the following information: a time course distribution of the complications; revision of the labeling to incorporate all applicable changes (e.g., indications for use, clinical results, complications); inclusion of sterilization instructions for the instrumentation in the labeling; modifications to the surgical technique manuals; generation of a surgeon training program; and development of the post-approval studies with specific elements.

FDA issued a letter to Spine-Tech, Inc. on June 20, 1996, advising that its PMA was approvable subject to the conditions listed above as recommended by the Panel and required by FDA.

In amendments received by FDA on July 26, August 12, and August 23, 1996, Spine-Tech, Inc. submitted the requested information. The company reanalyzed the clinical outcomes using the revised definition of overall patient success (redefined again to be

based on only fusion, pain, function, and muscle strength while capturing neurological information in the complication section), provided the time course distribution of complications, revised the labeling, described their surgeon training program, and developed two post-approval studies. The first post-approval study involves the collection of clinical and radiographic data for long term device performance and patient outcomes for an additional four years of follow-up (for a total of six years of postoperative data) on a subset of the IDE patient population; the goal is to obtain six years of postoperative data on a minimum of 100 patients per surgical approach. The second post-approval study involves the retrieval assessment of any BAK™ device that is implanted and subsequently removed.

In amendments received by FDA on September 11 and September 13, 1996, Spine-Tech, Inc. submitted the required information which included revisions to the labeling and post-approval studies and agreed to the conditions cited in the approvable with conditions letter dated June 20, 1996. CDRH determined that, based on the above modifications, the applicant's response was adequate.

FDA inspections completed on August 6 and 7, 1996, determined the manufacturing facilities to be in compliance with the Good Manufacturing Practices (GMP) regulations.

CDRH issued an approval order on _____.

XV. APPROVAL SPECIFICATIONS

Directions of Use: See labeling.

Hazards to Health from Use of the Device: See indications, contraindications, warnings, precautions, and adverse events in labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES FOR CONTROLS

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